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# The future of endothelin research: Scientific mentoring and beyond

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ABSTRACT

Endothelium-dependent regulation of vascular tone was one of the key discoveries in physiology in the 1980s, including the characterization of endothelium-derived vasoactive factors such as endothelin. Young investigators, often while starting research as part of their PhD degree, have been instrumental in carrying out the work that led some of the most important discoveries in the endothelin field. This article reviews the importance of mentoring for research in general and for endothelin research in particular, including examples of outstanding young investigators that have been instrumental in some of the key discoveries in the endothelin field. Recognizing scientific excellence among young investigators has a long tradition in the history of the International Conferences on Endothelin. Winners of "Young Investigator Awards" of the past five endothelin conferences (ET-8, ET-9, ET-10, ET-11, and ET-12) are presented, as well as recipients of the "ET-12 Best Presentation Awards" established on the occasion of the Twelfth International Conference on Endothelin ET-12 in Cambridge in September 2011.



## Introduction

The idea for this article originated from discussion between the authors at the Twelfth International Conference on Endothelin (ET-12), and the realization of how important new investigators have been in advancing the field of endothelin research and that future advancement of knowledge – not only in the endothelin field – similarly will continue to depend on the contribution of talented early career scientists. At the recent ET-12 conference in Cambridge, new investigators presented a large amount of the novel research findings, confirming that there still is a strong future of endothelin research. We thus felt it appropriate not only to recognize the prior awardees in an article, but also to put into perspective how contributions of the early stage scientists and their mentoring by senior researchers have been instrumental in advancing this field.

## How young investigators contributed to the discovery of endothelin

In keeping with the successful support of young investigators in the field of endothelin research for almost 25 years, many awards were presented to early career scientists at the Twelfth International Conference on Endothelin held at Clare College of the University of Cambridge, UK, September 11–14, 2011. Many of these individuals were presenting the fruits of their scientific work to an international audience for the first time. The field has now produced more than 25,000 publications (Fig. 1) since the work that led to the discovery of the sequences of the endothelin gene and peptides which started in May 1987 (Masaki, 1998), at the University of Tsukuba where Professor Tomoh Masaki — following the suggestion of a young investigator, who had just completed medical school and was about to start his Ph.D. dissertation research at age 27. This young investigator, Masashi Yanagisawa, proposed to his mentor – who agreed – to identify and characterize a vasoconstrictor peptide that had been described and published by another young PhD student at the time, Christine Hickey neé Agricola, who had first published an abstract on the subject in 1984 (Agricola et al., 1984) and shortly thereafter as a full manuscript (Hickey et al., 1985). In an effort to develop an idea for a thesis project, graduate student Kristine Hickey (née Agricola) had read with great interest the work of Furchgott and Zawadzki (1980) that led to the eventual awarding of the Nobel Prize for the discovery of endothelial derived relaxing factor, nitric oxide (NO) (Mitka, 1998). Of course at the time, no one knew it was NO and so Ms. Agricola decided that her project would focus on the identification of this putative endothelial-derived relaxing factor. Working under the mentorship of Professor Robert Highsmith in the Department of Physiology at the University of Cincinnati, Ms. Hickey developed the difficult procedure of culturing vascular endothelial cells, a less than trivial accomplishment for the time, and applied conditioned media to isolated vascular strips expecting to evaluate smooth muscle relaxation. However, she was plagued by a persistent problem that there was no relaxation, but rather, persistent constriction. After considerable time and effort, she

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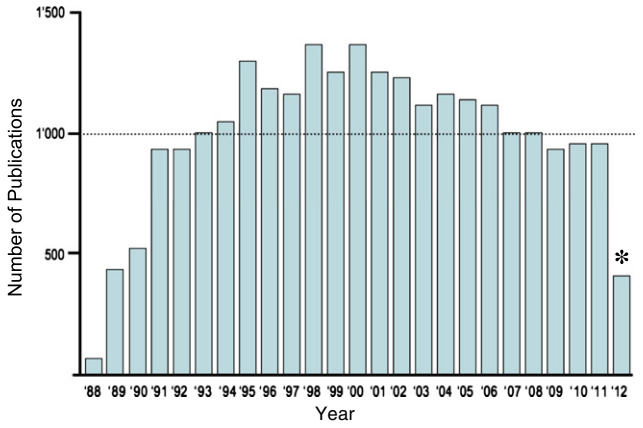


**Fig. 1.** Graphical illustration of number of scientific publications on endothelin listed in the Pubmed/NCBI database. Since 1988, more than 25,000 papers have been published, counting between 42 (1988) and 1409 (2000) publications per year. Data for 2012 (*) are shown for the period from January through May 2012. Information derived from http://www.pubmed.gov.

was able to convince her advisor, as well as her collaborators in the Department, Drs. Richard Paul and Gabor Rubanyi, that the endothelium produces a peptide capable of prolonged vasoconstrictor activity. To his credit as a mentor, Professor Highsmith allowed this young student to pursue her ideas despite the challenges both at the bench and with scientific dogma at the time. The importance of a mentoring team is also highlighted in this work by bringing together Highsmith's expertise in protein biochemistry and Paul and Rubanyi's vascular biology experience.

In a similar fashion, the young Dr. Yanagisawa took the findings of Hickey and colleagues (Hickey et al., 1985; Barton et al., 2012) and developed his own PhD thesis into what is now considered the "discovery" of endothelin that serves as a model for all graduate students — the isolation of the peptide, identification of its isoforms and biosynthetic pathway, and full *in vitro* and *in vivo* characterization. The work for Yanagisawa's Ph.D. project – with the support of many other scientists – had progressed so rapidly that after only half a year, a manuscript was submitted to Nature on December 1 of 1987, where it was accepted on January 29, 1988 and published on March 31 of the same year (Yanagisawa et al., 1988), This is example enough that none of the discoveries made at the beginning of the

**Table 1**
Recipients of the "ET-12 Young Investigator Awards", presented at the Twelfth International Conference on Endothelin (ET-12), Cambridge, United Kingdom, 2011.

| | |
|---|---|
| Christopher Adlbrecht | Austria |
| Hilda Ahnstedt | Sweden |
| Johny Al-Khoury | Canada |
| Caroline Archer | UK |
| Nur Arfian | Japan |
| Levon Avedanian | Canada |
| Oliver Baretella | Hong Kong |
| Simona Buelli | Italy |
| Ruha Cerrato | Sweden |
| Mila Cervar-Zivkovic | Austria |
| Karolina Duthie | UK |
| Samer-ul Haque | UK |
| Anggoro Budi Hartopo | Japan |
| Susi Heiden | Japan |
| Martin Houde | Canada |
| Kelly Hyndman | USA |
| Mollie Jacobs | USA |
| Mary Leonard | USA |
| Lowell Ling | UK |
| Merlijn Meens | The Netherlands |
| Clemence Merlen | Canada |
| Matthias Meyer | USA |
| Jelly Nelissen | The Netherlands |
| Karla Neves | Brazil |
| Hemanshu Patel | UK |
| Daniel Reed | UK |
| Monika Schlosser | Germany |
| Amit Shah | USA |
| Gregory Star | Canada |
| Yoko Suzuki | Japan |
| Jonathan Towler | UK |
| Nicolas Vignon-Zellweger | Japan |
| Melanie von Brandenstein | Germany |
| Alison Whyteside | UK |
| Bambang Widyantoro | Japan |


**Fig. 2.** Three generations of endothelin researchers representing an example of successful scientific mentoring presenting some of the ET-12 Young Investigator Awards (from left to right): Ms. Yoko Suzuki, Kobe Pharmaceutical University, Japan; Dr. Nicholas Vignon-Zellweger, Kobe Pharmaceutical University, Japan (back) ; Dr. Susi Heiden, Kobe Pharmaceutical University, Japan; Professor Noriaki Emoto, Kobe University and Kobe Pharmaceutical University, Japan; Professor Masashi Yanagisawa, University of Texas Southwestern, Dallas and University of Tsukuba, Japan; Dr. Bambang Widyantoro, University of Indonesia, Indonesia and Kobe University, Japan; Dr. Anggoro Budi Hartopo, Kobe University, Japan; Dr. Nur Arfian, Kobe University, Japan (photograph by Suzete Sandin, Sherbrooke).

**Table 2**
Recipients of the "ET-11 Young Investigator Awards", presented at the Eleventh International Conference on Endothelin (ET-11), Montréal, Canada, 2009.

| | |
|---|---|
| Rafaela Claudino | Brazil |
| Fernanda Giachini | USA |
| Aditya Goel | USA |
| Michelle Gumz | USA |
| Aisha Kelly-Cobbs | USA |
| Nicholas Kirkby | UK |
| Victor Lima | USA |
| Iain MacIntyre | UK |
| Merlijn Meens | The Netherlands |
| Cornelius Nwora | USA |
| Jbiran Weil | USA |
| Bambang Widyantoro | Japan |

field of endothelin research would have been possible without the suggestions, contributions, and hard work of these bright and persistent young investigators. Similarly, discovery of endothelium-vasoconstriction is owed to another PhD project, namely that of Jo De Mey at the University of Antwerp in Belgium (De Mey and Vanhoutte, 1981, 1982) who at that time worked under the supervision of Professor Paul M. Vanhoutte.

## Scientific mentoring in three generations of endothelin scientists

In 1987, Professor Masaki recognized the potential of his young investigator, Yanagisawa, who had joined his group for a Ph.D. thesis and whom he not only mentored but also for whom he provided considerable financial research support which allowed his mentee to finally get the anticipated results. Thus, Yanagisawa's own success is owed to successful mentoring by Masaki. It comes to no surprise that Yanagisawa stepped into the footsteps of Masaki and started mentoring his own trainees at the University of Texas Southwestern, which included Noriaki Emoto, Cheryl Gariepy, and Sabine Telemaque – all of which have made their own important impact on the field. Meanwhile, Emoto, who started as a graduate student with Yanagisawa and Masaki, has returned to Kobe University. In the tradition of his teachers, Emoto has now mentored the third generation of endothelin researchers, many of which were present at and received awards for their work at the ET-12 Conference (Fig. 2).

**Table 3**
Recipients of the "ET-10 Young Investigator Awards", presented at the Tenth International Conference on Endothelin (ET-10), Bergamo, Italy, 2007.

| | |
|---|---|
| Maria Fl. Albertoni Borghese | Argentina |
| Dyah Wulan Anggrahini | Japan |
| Saema Ansar | Sweden |
| Levon Avedanian | Canada |
| Alexa Bramall | Canada |
| Fernando Carneiro | USA |
| Inik Chang | USA |
| Dan-Dan Chen | USA |
| Jane Chiu | Canada |
| Marlen Damjanovic | Switzerland |
| Neeraj Dhaun | UK |
| Raul Ariel Dulce | Argentina |
| Carolina Garciarena | Argentina |
| Moinuddin Hoosein | UK |
| Subrina Jesmin | Japan |
| Laura Kennedy | Canada |
| Anna Konior | Poland |
| Christian Kreipke | USA |
| Daisuke Nakano | USA |
| Chantal Provost | Canada |
| Oleg Rayhman | Israel |
| Uliana Rushentova | Russian Federation |
| Stephanie Sauvage | Canada |
| Markus Schneider | USA |
| Alexandra Simonova | Russian Federation |
| Lisa Stow | USA |
| Renee Suen | Canada |
| Maria Fernanda Werner | Brazil |
| Bamgang Widyantoro | Japan |
| Lovro Ziberna | Slovenia |

## Special awards for early career investigators at endothelin conferences

In order to recognize scientific contributions of young researchers in the endothelin field the tradition has evolved at the International Conferences on Endothelin to recognize extraordinary talent through the presentation of Young Investigator Awards based on the scientific quality of submitted abstract (Tables 1–4). At the Cambridge conference, the Conference Chairs presented a total 36 "ET-12 Young Investigator Awards". These awards to young scientists from 11 countries from around the world (Fig. 4), included both financial support as well as a framed Award Certificate. As a novelty, following discussions with Dr. Irene Kanter, Publisher of Life Sciences at Elsevier, two newly created awards for young investigators were established at the ET-12 conference to recognize excellence for the delivery of both the best oral and best poster presentation at an endothelin conference. The awards not only include a 1 year subscription to the Elsevier journal Life Sciences, but also an invitation extended to the award recipient to contribute a regular review article on a subject related to their work in the endothelin field for publication in Life Sciences. Thus, the young scientist awardees will have the possibility to publish their work and to become internationally visible for their scientific achievement and expertise.

**Table 4**
Recipients of the "ET-9 Young Investigator Awards", presented at the Ninth International Conference on Endothelin (ET-9), Park City, Utah, USA, 2005.

| | |
|---|---|
| Suko Adiarto | Argentina |
| Farhad Amiri | Canada |
| Alan Bagnall | UK |
| Saema Beg | Sweden |
| Erika Boesen | USA |
| Florencia Borghese | Argentina |
| Carmen Bras-Silva | Portugal |
| Simona Buelli | Italy |
| Xiaoling Dai | USA |
| Phillippe Dauli | Canada |
| Louise Dawson | UK |
| Dorota Dajnowiec | Canada |
| Shaoqing He | USA |
| Jean-Claude Honore | Canada |
| Alison Hunter | UK |
| Naoko Iwasa | Japan |
| Subrina Jesmin | Japan |
| Nick Kelland | UK |
| Rajesh Kumar | USA |
| Yanny Elizabeth Lau | USA |
| Imtiaz Mawji | Canada |
| Dita Maixnerova | Czcheslovakia |
| Augusto Monezano | Brazil |
| Erin Mueller | Canada |
| Gregor Mueller | Germany |
| Kamashki Sachidanandam | USA |
| Victoriya Petrukhina | USA |
| Suno Raharjo | Japan |
| Jennifer Sasser | USA |
| Stephanie Sauvageau | Canada |
| Amit Saxena | Germany |
| Nobutake Shimojo | Japan |
| Francesca Spinella | Italy |
| Renee Suen | Canada |
| Keshari Thakali | USA |
| Errol Thomson | Canada |
| Ildiko Toma | Hungary |
| Charlotte Waters | UK |
| Corinne Widmer | Switzerland |
| Alvaro Yogi | Brazil |


**Fig. 3.** ET-12 Young Investigator Award Recipients after the ET-12 Award Ceremony at The Riley Auditorium, The Gillespie Centre, Clare College, The University of Cambridge (photograph by Suzete Sandin, Sherbrooke).

At the ET-12 conference, the inaugural "Best Presentation Awards" were given, and all oral and poster presentations were judged by a multi-national Awards Committee headed by Dr. Pedro d'Orléans-Juste, who at the end of the meeting communicated the decisions of the Awards Committee to the conference chairs. Much to everyone's surprise, the first "Best Presentation Awards" both went to one and the same young researcher, Dr. Melanie von Brandenstein of the University of Köln, Germany (Fig. 4). Dr. Brandenstein is working in the scientifically exciting area of microRNAs as novel regulators of gene expression and function and has been focusing on their role in regulating the functions of endothelin. As part of her award, Dr. Brandenstein was invited to submit an article reviewing the role of micro RNAs for endothelin function, which is also published in this issue (von Brandenstein et al., 2012).

Finally, in 2011 the Endothelin International Advisory Board has agreed to establish the biannual "Tomoh Masaki Award" (Barton et al., 2012) in recognition of the extraordinary contributions to science of Professor Masaki, which include the discovery of endothelins and cloning of the $ET_B$ receptor (Masaki, 1998; Sakurai et al., 1990; Yanagisawa et al., 1988), and importantly, recognizing him as a role model in successful scientific mentoring. The inaugural Tomoh Masaki Award in 2011 was presented to Masaki's former student, Professor Masashi Yanagiswa, at the ET-12 conference in Cambridge (Barton et al., 2012). The second Tomoh Masaki Award will be presented at

**Fig. 4.** The newly established Best Presentation Awards, sponsored by Elsevier Publishers, and inaugurated at the Twelfth International Conference on Endothelin, both went to Dr. Melanie von Brandenstein, University of Köln, Germany, shown here with Dr. Masashi Yanagisawa (photograph by Suzete Sandin, Sherbrooke).

*"I think really in order to keep this field of this highly exciting endothelin story going, each one of us should use their imagination in a positve way.*

*Especially for those young investigators:*

*Please do not simply follow the hypothesis given by your mentor or try to cast yourself into some preformed idea or dogma."*

Masashi Yanagisawa

The Twelfth International Conference on Endothelin
Cambridge, September 14, 2011

**Fig. 5.** Quote by Dr. Yanagisawa from his "Highlights of ET-12" lecture given on September 14, 2011 at the Twelfth International Conference on Endothelin in Cambridge.

ET-13 in Tokyo in September 2013 and the recipient announced at the conference.

## The future of endothelin research

At ET-12 in Cambridge, the Guest Editor referred to the Young Investigator Award recipients (Fig. 3) as "The Future of Endothelin Research." As with their predecessors Hickey (Agricola et al., 1984; Hickey et al., 1985), Yanagisawa (Yanagisawa et al., 1988), and De Mey (De Mey and Vanhoutte, 1981, 1982) the future of endothelin research will continue to depend on the curiosity, creativity, and dedication of young scientists to advance the field to a similar degree as before. In order to achieve personal joy from science and to follow on paths others have begun to lay out, the young shapers of the future of endothelin research will need to show independence in thinking, being creative, and the willingness to question dogma if necessary in order to advance knowledge, as Professor Yanagisawa so elegantly put it at the beginning of his summary of the highlights the ET-12 conference (Fig. 5) (also see (Yanagisawa Lecture) for a video recording of his lecture). Yanagisawa's advice should be taken seriously by any young scientist in endothelin research and beyond and may well be a generally applicable formula that will help to pursue scientific questions in a way that future knowledge will be uncovered. Satisfaction in this business comes from knowing that your work, however seemingly small at the time, helped to move the field forward. Often that impact is not known at the time, but is revealed as the field develops. From a mentor's perspective, leaving a greater legacy for future generations is as significant an accomplishment as any publication.

The field of endothelin research has a long history of cooperativity and collegiality among investigators and allowing the quest for knowledge to drive the discussion, as is characteristic of the endothelin conferences. This has created an environment where the young investigators are welcomed and encouraged. Needless to say, the accomplishments of the trainees and early career investigators have made this a vibrant field of research that will continue to impact the field of biology and medicine for years to come.

### Conflict of interest statement

None.

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